Tetrahedron Letters, Vol. 33, No. 18, pp. 2455-2458, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

STEREOSELECTIVE SYNTHESIS OF SYN-1,3-DIOLS

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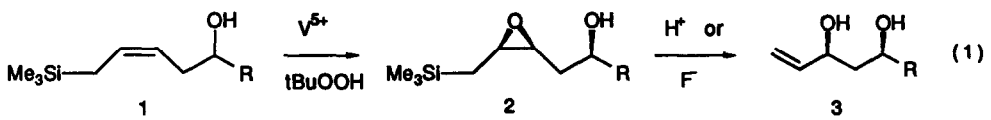
Summary: Z-allylsilanes 1 are epoxidized by V^{5+}/TBHP with high erythro-selectivity (up to 97:3) . HF- or TBAF-induced fragmentation leads to syn-1,3-diols 3. Compound 3f can be transformed within two steps into a key synthon for the lactone moiety of compactin.

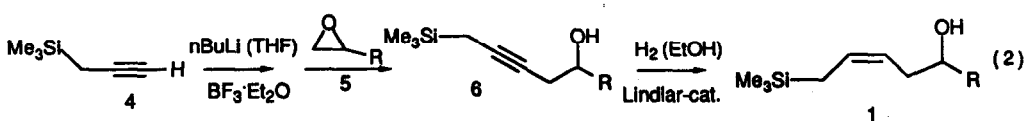
Key-Words: Epoxidation, syn-1,3-diol, Pig Liver Esterase

Functionalized diols of defined stereochemistry are valuable synthetic intermediates. A few years ago we reported an epoxidation-fragmentation process of Z-allylsilanes 1 which yielded syn-diols of general structure 3 (cf. eq.1).[1] However, this sequence could not compare favourably with established methods.[2] Although the 1,3-chirality transfer occurred quite efficiently, the exceedingly low isolated yields precluded its broad application. In this communication we disclose a markedly improved experimental procedure which roughly triples the yield. Furthermore we present additional examples which confirm the reliable syn-selectivity and help to explore the limits and scope of this methodology.



1 2 3 (1)

The substrates 1 were again readily prepared from the now commercially available propargyl-trimethylsilane[3] 4 and the corresponding epoxides 5 (cf. eq.2). Under Yamaguchi conditions[4] attack of the sp-carbanion occurred almost exclusively[5] at the less substituted carbon of 5.[6] However, in the case of 5e an unseparable 82/18 mixture of both regioisomers[7] was isolated. Hydrogenation over Lindlar catalyst occurred smoothly at RT and atmospheric pressure to yield the desired Z-allylsilanes 1 nearly quantitatively[8].

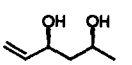
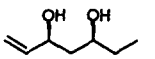
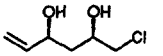
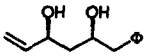
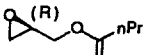
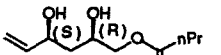
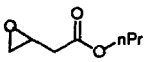
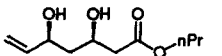
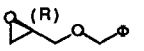
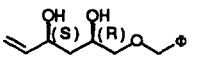
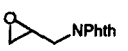
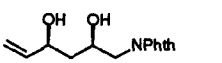
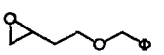
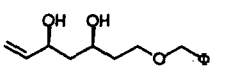


4 5 6 1 (2)

Epoxidation was performed following the slightly modified Mihelich procedure[9] (toluene as solvent, 1.5 eq. of tBuOOH (TBHP), 0.05 eq. of VO(acac)$_2$, -15°C - RT, 15h). The disappearance of the starting material could be followed by TLC. After completion of the reaction the remaining TBHP was destroyed by adding 3 eq. of $(MeO)_3P$. Afterwards fragmentation of the labile epoxides was induced within the same reaction flask by either addition of 3 eq. of nBu_4NF in THF (method A) or by introducing an excess of HF in CH_3CN (methodB).

After stirring at ambient temperature for 30 min, standard aqueous work up followed by flash chromatography allowed the isolation of the 1,3-diols 3 as syn-/anti-mixtures in consistently reasonable yield (cf Table).

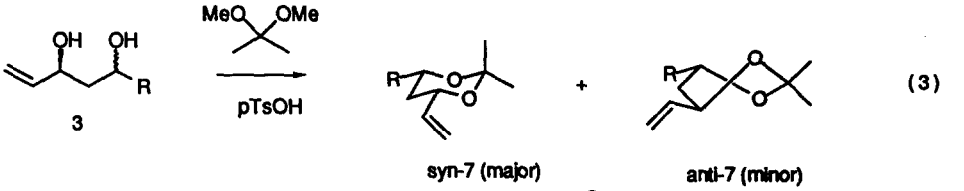
TABLE Diastereomeric Ratios from the V^{5+}-Catalyzed Epoxidation of Allylsilanes 1

Entry	Epoxide 5[a]	1,3-Diol 3[a]	Method[b]	Yield[c](%)	syn /anti[d]
1	 5a	 3a	A	70	95.5/4.5
2	 5b	 3b	A	61	97/3
3	 5c	 3c	B	68	93/7
4	 5d	 3d	A	74	97/3
5	 5e	 3e	A	51[e]	95/5
6	 5f	 3f	A	57	95/5
7	 5g	 3g	A	63	94/6
8	 5h	 3h	B	70	95/5
9	 5i	 3i	A	69	93/7

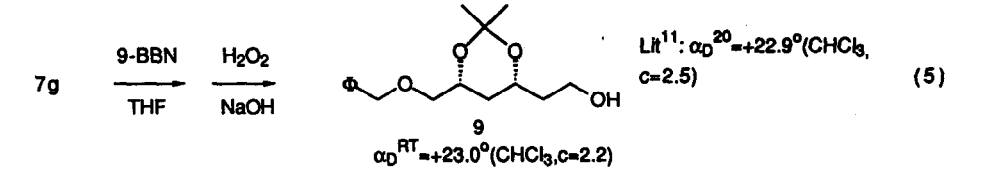
[a]All compounds are racemates except those in entry 5 and 7; [b]method A: fragmentation induced by nBu_4NF; method B: fragmentation induced by HF; [c]combined isolated yield of syn- and anti-diol 3 with regard to allylsilane 1; [d]ratios determined by GC-analysis, see text; [e]corrected yield (starting 1e only 82% pure).

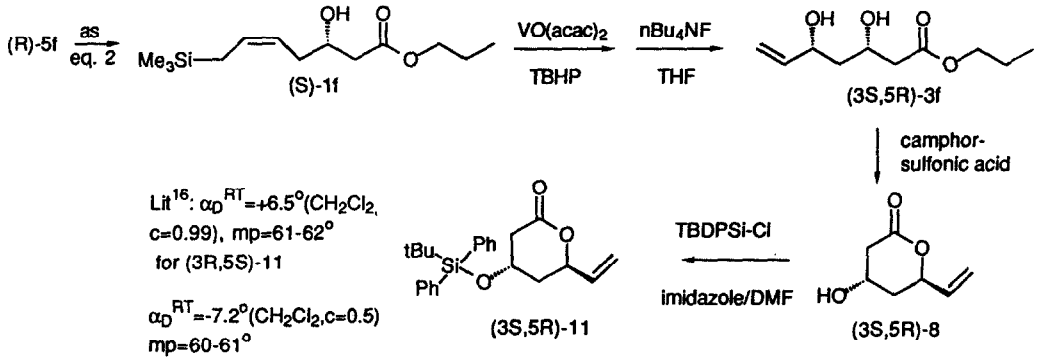
For accurate determination of the diastereomeric ratio all diols except 3f were transformed by treatment with 2,2-dimethoxypropane/pTsOH into the corresponding acetals 7 (eq.3) which were analyzed by capillary-GC (crosslinked methyl silicone). All (minor) anti-isomers eluted faster and base line separated from the main product syn-7. Configurational assignment was unambiguous due to ^{1}NMR spectroscopy of 7, the well established

erythro-selectivity of the epoxidation process[9], our earlier experience[1] and, finally, due to the synthesis of two intermediates of known stereochemistry (vide infra). **3f**, on the other hand, was analyzed at the stage of the β-hydroxylactone **8** (eq.4). The observed erythro-selectivity is generally high, irrespective of the size of R. Even the small methyl group affords synthetically useful ratios. Functional groups in the α- or β-position which might interact with the V^{5+}-center do, at most, slightly diminish the stereochemical outcome of the reaction.



As additional proof of the stereochemistry **7g** was hydroborated with 9-BBN to yield **9**[10] whose spectral properties were identical with those reported by Nicolaou[11] including the optical rotation (eq. 5)[12]. Epoxyester **5f**, on the other hand, was resolved by Pig Liver Esterase (E.C.3.1.1.1)[13] to afford (+)-**5f** besides epoxyacid (S)-**10** (eq. 6). ^{1}NMR-analysis in the presence of 1-(9-anthryl)-2,2,2-trifluoroethanol[14] revealed only one enantiomer indicating an e.e. of >90%[15]. Compound (+)-**5f** was then processed as above into (3S,5R)-**3f** which, upon treatment with camphorsulfonic acid, cyclized to the hydroxylactone (3S,5R)-**8**. Finally, silylation yielded the known intermediate **11**. NMR- and chiroptical properties compared favourably with the data given in lit.[16] for the enantiomer, an intermediate in the synthesis of compactin. As expected[13] PLE had cleaved epoxyester (S)-**5f** preferentially.





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3. From Fluka AG, Buchs, Switzerland.
4. M.Yamaguchi and I. Hirao, *Tetrahedron Lett.* 1983, *24*, 391.
5. Strict temperature control (<-70°C) during epoxide addition is essential for attaining high regioselectivity.
6. Yields depend upon the excess of Me_3SiCH_2CCH used; with 1.8 eq., typically 70-85% of **6** can be isolated.
7. Structural assignment based on GC-MS-analysis of the unseparable mixture of **5e**.
8. The samples of **1** were pure according to 250MHz ^{1}H-NMR and contaminated with less than 5% E-isomer, regioisomer or overreduced product.
9. E. D. Mihelich, K. Daniels, and D. J. Eickhoff, *J. Am. Chem. Soc.* 1981, *103*, 7690.
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12. In our hands **9** proved to be very prone to acetal-rearrangement in $CDCl_3$ (due to traces of HCl?), whereas it was stable in DMSO solutions. For determination of the optical rotation, $CHCl_3$ was passed through a short column of basic alumina prior to use.
13. P.Mohr, L.Roesslein, and Ch. Tamm, *Tetrahedron Lett.* 1989, *30*, 2513; E. Baader, W. Bartmann, G. Beck, A. Bergmann, H.-W. Fehlhaber, H. Jendralla, K. Kessler, R. Saric, H. Schuessler, V. Teetz, M. Weber, and G. Wess, *Tetrahedron Lett.* 1988, *29*, 2563.
14. W. H. Pirkle and D. J. Hoover, *Topics Stereochem.* 1982, *13*, 263.
15. Due to poor signal splitting the accuracy was not very high, although direct comparison with racemic **5f** was made.
16. Ch. F. Jewell, Jr. and J. R. Wareing, *United States Patent* 4,625,039; Nov. 25, 1986.

(Received in Germany 29 January 1992)